

## ***Remarks***

### ***I. Status of the Claims***

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendments, claims 143-171 are pending in the application, with claims 143, 144, and 159 being the independent claims.

### ***II. The Amendments***

Claims 143, 144 and 159 have been amended to recite "an increased proportion of nonfucosylated oligosaccharides." Support for the amendments can be found, *inter alia*, in the claims as filed and in the disclosure on page 38, lines 2-6, and in Figures 9A-E. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

### ***III. The Office Action***

The Examiner asserts that amended claims 143-171, which were submitted in the Amendment and Reply filed May 14, 2008, and which are directed to glycoengineered, recombinant antibodies having increased bisecting GlcNAc residues are independent and distinct from previously filed claims 109-110, 112-115, 118-121, 125-128, and 132-142 directed to glycoengineered recombinant antibodies having nonfucosylated glycan oligosaccharide structures. Moreover, because claims 143-171 are the only claims currently pending in the application and, according to the Examiner, are directed to a

nonelected invention, the Examiner considers the amendment to be noncompliant, and has refused to enter it. To support his assertion, the Examiner states that because Applicants have received an Action on the merits for the subject-matter presented in claims 109-110, 112-115, 118-121, 125-128, and 132-142, the subject-matter in these claims has been constructively elected by original presentation for prosecution on the merits. Accordingly, the Examiner believes a shift in invention occurred when the Applicants sought to cancel claims 109-110, 112-115, 118-121, 125-128, and 132-142 and add new claims 143-171. Applicants respectfully disagree. As explained by Applicants below, (1) no shift in invention occurred when claims 143-171 were amended, and (2) increases in bisecting GlcNAc glycan structures *necessarily* correlate with increases in nonfucosylated glycan structures since oligosaccharides that are first modified by GnT III/Gal T can no longer be biosynthetic substrates for core  $\alpha$ -1,6-fucosyltransferase.

***A. Shift in Invention (M.P.E.P. § 819, 821.03)***

Applicants wish to direct the Examiner's attention to M.P.E.P. § 821.03 which states:

The practice set forth in this section is not applicable where a provisional election of a single species was made in accordance with MPEP § 803.02 and applicant amends the claims such that the elected species is cancelled, or where applicant presents claims that could not have been restricted from the claims drawn to other elected invention had they been presented earlier.

Applicants believe the practice set forth in M.P.E.P. § 821.03 is not applicable as the new claims 143-171 presented in the May 14, 2008, Amendment and Reply could not have been restricted from claims 109-110, 112-115, 118-121, 125-128, and 132-142 as the subject-matter in claims 143-171 had in fact been presented earlier and the Office

had concluded that those claims are not directed to an invention distinct and independent from that previously presented.

In the Applicants' Preliminary Amendment of December 22, 2004, the Applicants presented independent claims that were directed broadly to glycoengineered, recombinant antibodies with altered patterns of glycosylation (claims 86-87) and dependent claims directed to both glycoengineered, recombinant antibodies that have increased bisecting GlcNAc residues (claims 95-97, 105, and 107), and glycoengineered, recombinant antibodies that have nonfucosylated glycan structures (claims 106-107).

While the Applicants did receive a first Office Action on the merits directly addressing claims 86-108, on April 12, 2005, Applicants did not receive a Restriction Requirement requiring an election of a subset of the claims for further prosecution. Conspicuously absent from the prosecution history of the present application is any issued Office Action mandating that the Applicants opt to either prosecute claims directed to glycoengineered, recombinant antibodies that have increased bisecting GlcNAc residues or prosecute claims directed to glycoengineered, recombinant antibodies that have nonfucosylated glycan structures. As the Applicants had presented claims directed to the subject matter of claims 109-110, 112-115, 118-121, 125-128, and 132-142 and claims 143-171 earlier on in prosecution and these had not been restricted out, the practice set forth in M.P.E.P. § 821.03 is not applicable here.

In any event, amended claims 143-171 maintain nonfucosylated language while incorporating the bisecting GlcNAc language from previously presented dependent claims (*e.g.*, claims 95-97, 105, and 107). Thus, amended claims 143-171 are not directed to an independent and distinct invention, but rather add a further limitation to the pending claims.

**B. Relationship Between Bisecting and Nonfucosylated Glycan Structures**

Applicants believe that the entry of claims 143-171 does not constitute presentation of a non-elected invention for another reason; glycoengineered, recombinant antibodies that have increased bisecting GlcNAc residues necessarily have decreased fucosylated (*i.e.*, increased nonfucosylated) oligosaccharides. When GnT III is overexpressed in host cells, decreased fucosylation of recombinant protein oligosaccharide structures ***necessarily*** results along with increased bisecting GlcNAc oligosaccharide structures.

**1. GnT III Overexpression Results in Decreased Fucosylation (*i.e.*, Increased Nonfucosylation)**

The present specification explicitly states that, when GnT III is overexpressed, oligosaccharide structures can no longer be substrates for the core  $\alpha$ -1,6-fucosyltransferase. *See* specification at page 38, lines 2-6. This was well-known in the field at the time of the invention. For example, Schachter *et al.* in Figure 3 (previously submitted as reference AS in an Information Disclosure Statement filed October 13, 2004) and the priority document explicitly state that "[t]he addition of fucose to the core of oligosaccharides can take place at any point after reaction 5 of the [central reaction network of the N-linked glycosylation pathway], **but it is also blocked by the modifications that GalT or GnTIII introduce.**" *See* Schachter *et al.*, *Biochem. Cell Biol.* 64:163-181 (1986) and Priority Document at page 17, lines 28-30. Thus, the priority document also identifies a relationship between GnT III expression and a reduction in core fucosylation. If the core fucosyltransferase cannot add a fucose residue to the core oligosaccharide structure, there will be an increased proportion of

nonfucosylated oligosaccharides. Thus, GnT III overexpression necessarily results in decreased fucosylation (*i.e.*, increased nonfucosylation).

**2. GnT III Overexpression Commits Recombinant Antibody Oligosaccharides to Bisecting Glycan Structures**

Applicants wish to direct the Examiner's attention to Figure 11 of the present application and Schachter *et al.* which describes a composite scheme for the biosynthesis of N-glycosyl oligosaccharides based on *in vitro* assays carried out in different tissues. Schachter *et al.* state that M<sub>5</sub>Gn "can be acted on by (i) GlcNAc-transferase III to form bisected biantennary five-Man hybrids" and that once "the bisecting GlcNAc has been inserted by GlcNAc-transferase III,  $\alpha$ -mannosidase II can no longer act [(45)] and the pathway is fixed into the production of hybrids." This statement is consistent with Figure 11 of the present application which shows that once GnT III acts on M<sub>5</sub>Gn, M<sub>4</sub>Gn, or M<sub>3</sub>Gn, the biosynthetic pathway is committed to producing only bisected hybrid structures.

Accordingly, overexpression of GnT III in a host cell results in recombinant antibodies that not only have increased bisecting GlcNAc residues but also an increased proportion of nonfucosylated oligosaccharides.

However, not in acquiescence to the rejection, Applicants have amended claims 143, 144, and 159 to recite "an increased proportion of nonfucosylated oligosaccharides."

Applicants believe that a full and complete reply has been made to the outstanding Notice of Non-Compliant Amendment (37 C.F.R. § 1.121). Accordingly, Applicants request entry of the above Amendment, and entry of the Amendments filed on May 14, 2008 (incorporated herein by reference).

Based on the Amendment and Remarks filed on May 14, 2008, and the present Amendment, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

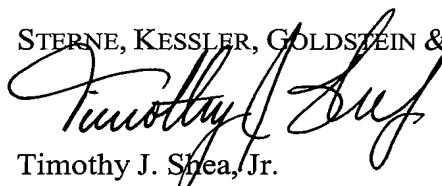
***Conclusion***

All of the state grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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